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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,618	02/06/2004	Thomas W. Dubensky JR.	282172002800	8471

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

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10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,618	DUBENSKY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,83-92,95-123 and 127-149* is/are pending in the application.

4a) Of the above claim(s) *108 and 139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,83-92,95-107,109-123,127-138 and 140-149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 7/26/07 is made. Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149, elected species uvrA and uvrB, were previously under examination. Claims 88-96 and 119-127 have been canceled. Claims 108 and 139 were previously withdrawn from consideration.

Accordingly, claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 are currently under examination.

Information Disclosure Statement

1. The information disclosure statement filed 7/26/07 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It has been placed in the application file, but the information referred to therein, e.g., under 'Foreign Patent Documents' and 'Non-Patent Literature Documents' has not been considered.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed..Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 20-21 and 83-87, 97-107, 109-118, 128-130, 131--138 and 139-149 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32, 33, 60, 66, 90, 94, 101 and 103 of copending Application No. 11/173,770. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims are broadly drawn to an attenuated Bacillus bacterium which is attenuated for nucleotide excision repair. The later claims specify that this is due to mutations in the uvrA, uvrB, uvrC genes. Methods of inducing an immune response in a host comprising administering to the host an effective amount of a vaccine composition comprising a bacterium of this strain are recited. 'Vaccines' inherently provide 'protection'/prevent and therefor preventing or treating disease methods are also encompassed by these claims. The instant claims are drawn to methods of inducing an immune response (and preventing or treating a disease) in a host comprising administering to the host an effective amount of composition comprising a bacterium with the same mutations, particularly one or

more mutations in the uvrA, or uvrB genes. The instant dependent claims provide that the microbe is Bacillus anthracis. Accordingly, the claims are not patentably distinct from one another as the co-pending claims are included in the Genus of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 21 are vague and confusing because it is unclear what is meant by "reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active" because it is unclear which 'nucleic acid' is being targeted. A bacterium comprises numerous different nucleic acids encoding a multitude of different gene products. Accordingly, the metes and bounds of the invention cannot be understood. Further, which 'gene expression' is active? Again, there are so many different genes being expressed by the bacterium. Does the claim intend for all genes, including the nucleic acid which is targeted, to be actively expressed. The specification seems to indicate that the targeted

DNA is rendered incapable of gene expression after contact with the compound. Clarification and correction is requested.

Claims 20 and 21 are also vague and confusing because the structure/source/identification of the microbe is unclear. The claims only require that the microbe has been "modified by reaction with a nucleic acid targeting compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation". The mere recitation of vague process with an unspecified compound to describe the product to be used in the method is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, such as the type of microbe and the type/location of mutation, which would allow for one to identify the compound to be used in the claimed methods without ambiguity. Clarification and correction is required.

Claims 20 and 21 are also vague and confusing due to the term 'nucleic acid targeting compound' because it is unclear what class of compounds are encompassed by this language. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim Rejections - 35 USC § 112-Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "methods of inducing an immune response to a heterologous antigen in a host comprising administering an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterlologous antigen"; "methods of treating disease caused *by L.monocytogeneis* in a host comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation" and "a method of inducing an immune response to a heterologous antigen in a host comprising administering ,an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrABgene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterologous antigen" and does not reasonably provide enablement for "A method of preventing or treating a disease in a host, comprising administering to the host an effective amount of the vaccine of claim 1 a vaccine comprising *any* modified bacterium microbe, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid

so that the microbe is attenuated for proliferation, relative to the bacterium prior to modification, and wherein the modified bacterium expresses the antigen" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, and wherein the microbe expresses the antigen." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to "A method of preventing or treating a disease in a host, comprising administering to the host an effective amount of the vaccine of claim 1 a vaccine comprising ***any*** modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a *nucleic acid targeted compound* that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising ***any*** free-living microbe, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, and wherein the microbe expresses the antigen."

These claims encompass an incredibly large number of bacterium with an incredibly large number of different modification possiblities. The use of any 'nucleic

acid targeted compound' is also included which can attenuate proliferation by any means.

The instant specification has shown that microbial vaccines could be made exquisitely sensitive to killing by treatment with S-59 psoralen and UVA light. Mutant strains of Listeria monocytogenes were made unable to repair psoralen-DNA corsslinks by deleting the ultraviolet light resistance uvrAB genes which are required for nucleotide-excision repair. It was shown that Listeria monocytogenes uvrAB mutants were much more sensitive to S-59/UVA light inactivation as compared with the parental Listeria monocytogenes strain having intact DNA repair. These mutant, inactivated Listeria monocytogenes uvrAB mutants maintained their metabolic activity and were able to synthesize and create new protein. As a result, these Psoralen/UVA treated Listeria monocytogenes uvrAB mutants retained full ability to infect dendritic cells, escape from the phagolysosome and program presentation of antigen via the class I pathway. Examples 15 and 16 provide successful treatment results using the vaccines comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 and ultraviolet light.

In the present case, the applicant has neither provided any direction or guidance, nor any working examples in the specification as to any potential mutations of genes from other microbes (viruses, parasites), other species of bacteria (other Listeria species) or other Genus of bacteria that would satisfy the limitations of the claims. The claims read on any mutation to the uvrA and uvrB genes, and to homologs thereof, that have the effect of decreasing the activity of the gene product. Just as the breadth of the

claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation. Salmonella, Shigella, M.tuberculosis and Bacillus anthracis are recited in the dependent claims yet the specification fails to show that these bacterium would work in a similar manner. It is unclear of the sequence of the uvrA, uvrB genes in the Salmonella, Shigella and M.tuberculosis and they are extremely different from L.monocytogenes. It is unclear that they would behave in the same manner, e.g., become attenuated in a manner that leads them extremely sensitive to killing yet still maintained their metabolic activity and were able to synthesize and create new protein in response to treatment with psoralen and UVA irradiation. No experimental results are provided for the B.anthracis mutants. B.anthracis is a highly infectious bacterium and it is unclear that the attenuation would result in a non-toxic/lethal bacterium. A sporeless strain is not recited in the instant claims.

The instant fails to demonstrate that any compounds, other than psoralen, would result in an attenuated bacterium which would result in a non-virulent/toxic bacterium which would maintain its metabolic activity and still be able to synthesize and create new protein in a sufficient amount. Experimental results are only shown with respect to

psoralen and it would take one of skill in the art undue experimentation to discover and test other nucleic acid targeting compounds and the efficacy of the resultant vaccines.

While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the mutation recited in the claims, but the bacterium must be mutated in a certain way in order to attenuate the bacteria in a functional manner, e.g., psoralen and UVA treatment. The specific mutation(s) of the polynucleotide sequence to

accomplish decreased biological activity of the encoded polypeptide and the manner of attenuation, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Given the complexity of the art, the breadth of the claims, the number of potential mutations in different microbial mutants, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of uvrA and uvrB to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to

have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants argue that they have shown examples with B.anthracis mutants, yet no results for a method which demonstrates protection against anthrax or symptoms related to B.anthracis infection, as required by the scope of the claim, e.g, treating or preventing, are included in the instant specification, nor are working examples provided for treating or preventing E.coli infection. Applicants argue that modification with psoralen (S59) and UVA was widely known and effective in inactivating a wide variety of bacteria in the prior art at the time the invention was made. These arguments are not commensurate in scope with the claimed invention. This is one compound, not *any* nucleic acid targeted compound. Further, these references do not demonstrate prevention or treating a disease as is claimed. Applicants argue that making uvrA and uvrB mutants from any bacterium would be fully enabled, yet these arguments are not commensurate in scope with the claimed invention which is drawn to **a method of treatment or prevention of *any* disease** comprising the use of any modified bacterium which has been modified by ***any* nucleic acid targeted compound** which reacts with ***any* nucleic acid of the bacterium** to cause attenuated proliferation. There is no mention of a specific compound to be used or even a specific gene which is to be

targeted. These claims broadly read on an infinite number of genes, bacterium, diseases, etc. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Claim Rejections - 35 USC § 112-Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to "A method of preventing or treating a disease in a host, comprising administering to the host an effective amount of the vaccine of claim 1 a vaccine comprising ***any*** modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a *nucleic acid targeted compound* that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising ***any*** modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, and wherein the microbe expresses the antigen." The elected species read on mutations of the uvrA or uvrB genes or both genes, attenuated bacteria comprising such polynucleotides, and species homologs thereof. However, the specification does not provide adequate written description to support methods using either species homologs to the L.monocytogenes mutants, or any mutation/attenuation resulting in the desired phenotype and attenuation.

There is inadequate written description to support claims to species homologues of the disclosed polynucleotide for use in methods of treatment or prevention of any disease.

The claims are broadly drawn to obtaining attenuated microbes by mutating variant nucleotide sequences from many different species of organisms, e.g., viruses, parasites, multiple genus/species of bacterium, yet the specification has only shown an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which

has been attenuated by treatement with psoralen S-59 and ultraviolet light irradiation wherein the mutant bacterium expresses the heterlologous antigen" with respect to the elected species.

More than a statement of biological function is required to satisfy the 112 1st paragraph written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chugai, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." Id., at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id., at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." Id. Thus, it is clear that identification of polynucleotide by naming the polypeptide it encodes is not sufficient. In

the present case, the only description that the applicant has provided for species homologues of uvrA and uvrB is that they must also encode uvrA and uvrB proteins. Such a description is clearly insufficient to support the claimed genus. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the uvr gene's coding regions to target for modifications, in order to produce an attenuated bacterium. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an attenuated bacterium, once the molecule has been identified as necessary for the virulence of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et al., Science 247:1306-1310, page 1306. Bowie et al. presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states first that proteins generally accept a wide variety of substitutions in their residue sequence. However, it also states that some residues may not be substituted at all without loss of the proteins function. The reference also states that the effects of such substitutions are, currently, highly unpredictable. Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity.

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description and enablement requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

Applicants are claiming bacteria and they are claiming said bacteria comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. "The Applicant's are not claiming polynucleotide sequences per se."

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the coding sequence of uvrA and uvrB polynucleotide sequence, but the bacterium must additionally be mutated in such a way to attenuate the bacteria to desired effect. The polynucleotide sequence, as well as the specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Response to Applicant's Arguments:

Applicants argue that a variety of genes in a variety of different bacteria genuses had been identified at the time of filing that could serve as targets for attenuating mutations that would attenuate the ability of the bacteria to repair its modified nucleic acid. This argument has been fully and carefully considered but is not commensurate in scope with the claimed invention. There is no limitation in claims 20 or 21 which require

the targeted nucleic acid to be for a gene responsible for repair of DNA. There are many genes in a bacterium which if altered or deleted could cause attenuated proliferation and they are not necessarily 'repair genes'. Applicants focus on uvrA and uvrB mutants, but these are not recited in the bulk of the claims. Applicants continually cite psoralen (s59) and UVA as the nucleic acid targeted compounds, but are silent as to the numerous other possibilities. The claims are not limited to these compounds and lack written description for the breadth included in the claims. The specification does not adequately support the breadth of all of the claims that are presented. It cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and the claims are too broad because they may include many inoperative species. Applicants state that they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention. They state that biological properties typically vary, and that their specifications provide for evaluation of the effectiveness of their numerous modified bacterium for treatment or prevention of any disease. It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. See, e.g., Enzo Biochem, 296 F.3d at 1327-28 (remanding for district court to determine "[w]hether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); Lilly, 119 F.3d at 1569 (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling

within the scope of the genus" had not been provided); In re Gostelli, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (two chemical compounds were insufficient description of subgenus); In re Smith, 458 F.2d 1389, 1394-95 (CCPA 1972) (disclosure of genus and one species was not sufficient description of intermediate subgenus); In re Grimme, 274 F.2d 949, 952 (CCPA 1960) (disclosure of single example and statement of scope sufficient disclosure of subgenus).

Claim Rejections - 35 USC § 102

10 The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 20, 21, 83, 85, 86, 100, 110, 111, 112, 114, 116, 117, 131, and142 are rejected under 35 U.S.C. 102(e) as being anticipated by Agrewala et al (US2002/0136738 A1) published 9/26/02.

Agrewala et al disclose a vaccine with attenuated Salmonella. In example 3, the Salmonella are grown in macrophages (antigen-presenting cells) which are attenuated by exposure to the alkylating agent mitomycin C and gamma radiation. The attenuated bacterium (modified bacterium) present in the macrophages are then used as a vaccine.

The reference teaches that dendritic cells are the preferred antigen-presenting cells. The reference also disclose that Mycobacterium tuberculosis is grown in macrophages and exposed to an agent (isonizid) acting on the nucleic acid. The macrophages comprising the M.tuberculosis are used as a vaccine.

Response to Applicants' arguments:

Applicants argue that the reference does not teach administration of a compound (vaccine) comprising a modified bacterium, wherein the nucleic acid of the bacterium ahs been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active. This has been fully and carefully considered but is not deemed persuasive. The Salmonella are grown in macrophages (antigen-presenting cells) which are attenuated by exposure to the alkylating agent mitomycin C and gamma radiation. The attenuated bacterium (modified bacterium) present in the macrophages are then used as a vaccine. The reference teaches that dendritic cells are the preferred antigen-presenting cells. The reference also disclose that Mycobacterium tuberculosis is grown in macrophages and exposed to an agent (isonizid) acting on the nucleic acid. As stated above, the claims fail to make clear which gene expression in the modified bacterium is active, e.g., it seems that the targeted sequence would not produce an active expression of the gene product. The Salmonella are grown in macrophages (antigen-presenting cells) which are attenuated by exposure to the alkylating agent

mitomycin C and gamma radiation would inherently contain some active gene expression. The reference adequately addresses the broad scope of the claims.

12. Claims 20, 83, 85, 97, 110, 111, and 112 are rejected under 35 U.S.C. 102(b) as being anticipated by BASF AG(WO 89/09616).

The reference discloses Vibrio anguillarium strains which are attenuated by alkylating agents (mitomycin C, methylmethane sulfonate; pages 4-5) and which are used as a vaccine.

Response to Applicants' arguments:

Applicants argue that the reference does not teach administration of a compound (vaccine) comprising a modified bacterium, wherein the nucleic acid of the bacterium ahs been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active. Applicants argue that the reference does not teach mutating the strain which is to be used as the vaccine strain, but instead mutates the parent strain. They further argue that 'even if BASF AG taught that the mutant progeny of such a bacterium reacted with the mitomycin C or methylmethane sulfonate were to be used in a vaccine, the reference would still fail to teach "a vaccine comprising a modified bacterium, wherein the nucleic acid of the bacterium has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active."

These arguments have been fully and carefully considered but are not deemed persuasive. The claims are drawn to methods, not compounds. Additionally, the term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The passage Applicants refer to recite that the parent strain (which is the 'wild-type strain') is contacted with the mutagen and then becomes the mutant strain to be used in the methods. Accordingly, the reference applies. It is irrelevant that the reference refers to other multiple methods of mutating a bacterium, e.g, natural isolation, etc., as long as it teaches the claimed invention. The bacterium would inherently possess the functional characteristics of being is attenuated for proliferation relative to the bacterium prior to modification.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 20, 21, 83, 84, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 128-130, 136, 140-142 and 145 are rejected under 35 U.S.C. 103(a) as being unpatentable over AKZO (WO 02/40046) in view of Sander et al (Infect. Immun. June 2001. 69(6): 3562-3568) and Ferguson et al (Mutation Research. 1987. 184: 13-21).

Akzo discloses a Salmonella vaccine which is attenuated by a first mutation, the nature of which is not relevant (page 4, line 27) e.g. a mutation in a gene involved in the synthesis of the O-polysaccharides (strain 9R) or a mutation in the aromatic pathway of the bacterium (strain SL6261) and a second mutation, which prohibits the production of a functional RecA protein. Akzo discloses (page 4) that the mutation of RecA does not impair the already attenuated strain to adequately trigger he immune system but that the mutation of a recA gene impairs the ability of the bacteria to recombine and to revert to a wild-type level of virulence (page 3). The refence's teachings differ from the claims regarding the type of first modification of the DNA leading to the attenuation. The technical problem to be solved is the provision of an alternative first method of attenuation, which was used in the present application by using a psoralen compound activated by UVA irradiation. However, instant claims 20, 21, 83, 84, 97, 98, 99, 110, 111, 112, 114, 115, 116, 117, 128-130, 136, 140-142 and 145 do not require the use of psoralen compound activated by psoralen for attenuation.

Furthermore, since AKZO states that the type of first mutation is not relevant, a person of ordinary skill in the art would use a non-gene-specific method of attenuation such as the methods taught by Sander et al which show that a recA deletion mutant of Mycobacteria bovis has an increased susceptibility to DNA-damaging agents like the alkylating agent EMS and MMS. Sander et also show that the deletion of recA does not reduce the viability of the bacteria. Furthermore, the teachings of Sander et al indicate that recA mutants of Mycobacterium bovis are candidates for antigen delivery systems to express foreign antigens. Additionally, as uvrA, uvrB are well known in the prior art as

enzymes responsible for DNA repair, see Ferguson et al, they represent an obvious functional alternative for recA.

Response to Applicants' Arguments:

Applicants argue that the reference does not teach administration of a compound (vaccine) comprising a modified bacterium, wherein the nucleic acid of the bacterium ahs been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the modified bacterium is attenuated for proliferation relative to the bacterium prior to modification, wherein gene expression in the modified bacterium is active. This has been fully and carefully considered but is not deemed persuasive. Applicants argue the passage referred to in the rejection recites that the parent strain is contacted with the mutagen and not used in the methods. This is not persuasive as it appears the reference refers to the parent strain in the manner of the 'wild-type strain' which is contacted with the mutagen and then becomes the mutant strain to be used in the methods. Accordingly, the reference applies. Alternatively, it would have been prima facie obvious that the parent strain after mutation (in Applicant's sense) could be used in the methods, absent evidence to the contrary, because one of ordinary skill in the art would expect it to have the identical properties of any strains derived from it. The bacterium would inherently possess the functional characteristics of being is attenuated for proliferation relative to the bacterium prior to modification.

Status of claims

15. Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 are **not** provisionally rejected on the ground of nonstatutory obviousness-type double patenting

as being unpatentable over claims 39 and 40 of copending Application No. **10/773,792** because the claims are drawn to mutants with completely different mutations. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. *However, this rejection may apply if amendments are made to the claims of either application*.

The claims are also not rejected under double-patenting with respect to co-pending application **10/883,599** because that application no longer recites any method claims. If that application rejoins any method claims, a double-patenting rejection may be necessitated because the compositions read on the compositions used in the claimed methods.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the

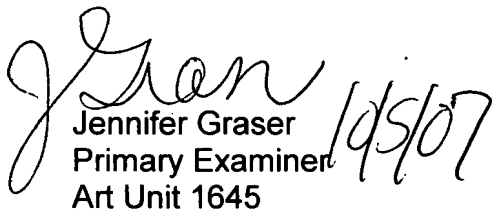
Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.



Jennifer Graser
Primary Examiner
Art Unit 1645